DR. DIAMOND: We have been given five questions we have been asked to discuss, the first of which you see on the screen in the front of the room, which is that valid scientific evidence is defined by the FDA as well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and, fifth, reports of significant human experience with a marketed device.

The first question for us is, what is the appropriate study design for devices that treat uterine fibroids using the above technologies. I would just remind the panel, again, that although most of the presentations we have heard this afternoon have related to uterine-artery embolization, there are actually a whole host of different approaches that are now coming into our specialty and for the FDA, which is really what our discussion is to be about, not specifically uterine-artery embolization.

So I would open to the panel, what should be the appropriate study design.

DR. PENTECOST: I am Michael Pentecost. I have a lot of respect for the RAND Corporation. I thought their comments were quite good. And I agree with most of them. I think the idea of a prospective multicenter trial is a good idea. I think most of us who have practiced for very long

have seen new technologies come and go that couldn't really bear this kind of scrutiny. So I think that is an excellent idea.

I think the idea of creating a quality-of-life instrument that is valid, prospectively, on forever, is also a very laudable idea. I appreciate Ms. Pearson's comments about the fact that, while, certainly, physiologic measures of disease are important to physicians and scientists, we are trying to make these people feel better and we ought to take great pains to investigate that.

I think, also, the idea of a registry under whosever guise--I don't know--I think is also a good idea. My sense is that this procedure is going to spread it to the community pretty quickly and it would be good to have a way to make sure that the results that we are finding in two or three or four or five university or specialty hospitals are also translatable to the community. So I think that is good.

I disagree, however, pretty strongly with the idea of a randomized clinical trial. I think very few surgical procedures, which basically this is, have had to meet that kind of rigor before they were accepted. I think it is very impractical as the two patients here mentioned that someone who wants to have less invasive therapy, if they happen to randomize to surgery, I think would fall out of the trial

rather than continuing. So I think it is impractical.

I also, frankly, think it is ill advised. This procedure was only described four years ago. For example, in vascular surgery, which is the way I make my living, interacting with vascular surgeons, the carol patch was identified in the early 1900s. It wasn't a randomized trial, a vascular surgical procedure, until 1990.

Carotid endarterectomy has been discussed for thirty years before a randomized trial came out. The reason I think it is ill advised, particularly in this condition, is because consensus has not yet gelled around this procedure.

Let me give you two specific instances. I don't do this procedure but when I talk to people who do, I hear them disagree about the size of particles that should be used. Some people say you want to use small ones. Some people, very smart on both sides, say you ought to use large ones.

Suppose we insist on an NIH-sponsored, five-year, multicenter trial using big particles. And, as we are doing this trial, people in the community find out that the small ones are really better. We have wasted five years, a lot of money, a lot of time, for a study which is really not transferable or practical anymore.

I also hear radiologists talk a lot about whether

or not you want to follow these patients with ultrasound or MRI. Suppose, in our study, we say we are going to do it with MRI and, along the course of time, two or three years from now, we find out ultrasound is just much, much better. We have now got this five-year study underway with results that people will not believe.

So I think at this stage of development, only four years after the procedure was first described, it is vastly premature to say we need a randomized clinical trial now because consensus has not developed around legitimate parts of the study yet, namely particle size and method of imaging and, I am sure, many, many more that I am not knowledgeable about to discuss.

Thank you.

DR. LEVY: I think that any study we do--I agree that a randomized clinical trial is impractical. It doesn't serve women very well and I don't think it serves our purposes very well for collecting the kind of information we want. That is not to say that I don't think we need to do some studies.

I think, though, that the outcomes that we are looking for are quality-of-life outcomes. This is not a life-threatening disease for the most part, absent the rare patient with overwhelming hemorrhage. This is a quality-of-life concern. Patients, for the most part, make

a decision to have surgery or intervention for quality-of-life reasons as the consumers who spoke to us eloquently described.

So I think our outcomes should not be MRI outcomes. They should not be ultrasound outcomes. They should be quality-of-life outcomes, both beginning and end, and the outcome of the intervention, itself.

We are hearing about returning to work at a week, returning to normal function in two weeks. My vaginal-hysterectomy patients are back to work in a week and doing normal function at two weeks. With a certain motivation of the patient, we can get those kinds of outcomes in all kinds of interventions, which is not to say that that is average or normal.

But I do think we need to look at a matched control group of women who have chosen a different alternative. I think the issue with the STOP-DUB trial was well discussed by Dr. Cooper. We will not get patients for a randomized controlled trial and it would be silly of us to even consider trying to do that. But a trial is absolutely necessary and it should be a trial of practiced patterns as they exist so that we don't legislate what size particles nor do we legislate what the other surgical procedures are that women would choose.

Some will choose hysterectomy. Some will chose

laparoscopic hysterectomy. Some will choose myomectomy. We just need to collect the data on those things and we need to use the same instruments. I think the quality-of-life instrument, if it turns out to be a really good one, is a step in the right direction.

DR. SHIRK: I think this has a lot of parallels with some studies I was involved with starting in the early '80's which was the endometrial-ablation studies. Those certainly did not have control-group studies with them so there was no randomization. Certainly, they address some of issues as far as life-quality issues.

The other issues they basically looked at were, obviously, fertility issues. So the question here is, basically, do we need sterilization with this procedure, what are the indications for future fertility, basically some kind of a protocol on how much bleeding is decreased so there is some quantification.

Obviously, everything that has been done so far is just sort of non-quantified as far as the amount of decrease in menorrhagia. So I would agree that probably trying to do a controlled study, randomized study, is going to be about impossible to do on this issue. Historically, it is not something the FDA has done for a similar procedure.

DR. DIAMOND: Let me come down on the other side. In fact, this very panel has suggested, in the past, the

need for randomized clinical trial in endometrial ablation. The guidelines that we proposed for that are a case in point.

We did that with our first guidelines before any product was approved for their use. And then, after that, one product was approved for use and we came out with a second set of guidelines which were modified but which would allow the product that was already approved to serve as the control group.

So, in fact, we do have, as a body, as an advisory panel, examples of requiring that. There are other examples that have come before this group and the drug group. The studies that are being done for postoperative adhesion development, the randomized clinical trials. Studies which have looked at GnRH analogues, the agonists originally as well as the antagonists, are randomized clinical trials.

Another example; there is a study that is ongoing at our institution right now where we are one of the participating centers of a study funded by NIH to look at medical versus surgical treatment of dysfunctional uterine bleeding. Within the subsurgical group, there are substudies of hysterectomy versus supercervical hysterectomy.

So there are good examples of randomized clinical trials which exist within our specialty and which have come

before this panel before. So, to suggest that is not something that we can consider is, I think, erroneous.

I am jumping a little bit ahead here but the issue was brought up that there was a lack of consensus now. I think that is all the more reason we ought to be making a decision right now. Once there is consensus for a lot of issues in the appropriate place, it may be much harder to do.

I am not sure, though, that we are going to want to specify such things as particle size and imaging modality but maybe identify those as parameters that the sponsors will want to consider and let them choose which ones to do based on whatever their device or product happens to be and the particular issues that they would like to see addressed.

DR. ROBERTS: I guess I have to take issue. I don't think that a randomized controlled trial is going to work. I will be real honest with you. I just don't think it is going to work. I think what we probably might want to do is to take a lead from the Circulatory Device Panel where they have this same problem with abdominal aortic aneurisms with the new stent grafts as being a noninvasive, one day in the hospital, kind of thing and then the patients go home versus a standard triple-A repair which is, basically, a week in the hospital and a lot of pain and agony afterwards.

What they found was is that they couldn't get the

trial, the randomized controlled trial, going. It just didn't go anywhere. I think it is very similar to this other problem with the myolysis. It is very hard to get patients to say, you are going to go through a standard surgical procedure versus something that is, basically, much less invasive.

But what they ended up doing was to take cohort studies. So you pick a cohort of people, either before you start doing the noninvasive thing or patients that are similarly matched that end up getting a surgical procedure and you use that cohort to match against.

There are now two devices that have been approved by the panel based on that kind of study. That is probably what you are going to want to look at here because, again, one of the issues with this, which wasn't even an issue with the triple-A study is the fact that this material is already approved for the treatment of hypervascular tumors. It has that marketing label.

DR. DIAMOND: Other comments?

DR. BLANCO: I would like to make a comment. For those of the panel who have been here before with home uterine-activity monitor, I am having this deja vu all over again that we may end up in the same place five years from now over this issue.

For those of you who have not been part of that,

it has been the same issue; do you do a randomized controlled trial or it can't be done so we accept other measures. You could take the viewpoint FDA is regulating the product that is going to be put in the uterine artery. What do you need to do to regulate that?

You need to make sure it is safe, so there need to be some safety studies. And you need to be sure it is efficacy. What is efficacious? It blocks the uterine artery. You could take that very simplistic approach to say, that is all they need to be able to regulate it.

We are taking it a further step. What we are actually looking at is looking at the procedure, itself, and saying do we want to compare this procedure to other procedures. And then it becomes very difficult if you don't do it in a randomized controlled way because there are always going to be the question of the validity of the data once it comes out.

I am not suggesting that we narrow it down to just what is the product asking for an indication and what is the claim that will be made. I think we need to be careful of what we suggest because we may not get any answers despite a lot of work.

DR. LEVY: I think, though, George, compared to the--I mean, I lived through a lot of that along with you. There are certain very specific safety questions that I have

about the procedure that may very well be answered more in a registry view than any other kind of trial. The kinds of information I want to know about--I want to know about the sepsis issue. Two deaths in 1500 cases is not comparable to the hysterectomy data in that the hysterectomy data, number one, are old and, number two, includes patients who have cancer, who are quite elderly. It is a totally different patient population than the mid-forties to mid-fifties women, or mid-thirties to mid-forties women, with fibroids.

So the sepsis issue is a key issue, something very important that I think we need to look at. The pregnancy issue; I know of uterine rupture subsequent to this. I know that this procedure is being marketed to the public by some places as a uterine-sparing procedure that permits pregnancy.

That scares me a lot. So that is information we need to get at. We are not going to get at that in a randomized clinical trial randomizing to hysterectomy. It is not going to happen.

The third thing is the ovarian-function issue. Six-month data, one-year data, is not good enough. The data about hysterectomy and loss of ovarian function is quite long-term. It is the British data that shows us that, through the remainder of a woman's life, she may become menopausal four, five years younger than she would have

otherwise.

That is not data we are going to get at in a randomized clinical trial, either. So I think we need to look at what are the safety questions we really need to ask, and those are questions that 400 patients or 500 patients are not going to answer for us because the incidence of these complications is going to be too low.

But we would have to be looking at thousands of patients to answer these kinds of questions. Therefore, I think it is impractical. I just don't think it is going to answer--the registry that you guys are doing is a better way to answer some of those things and then using concurrent cohorts to compare them, I think, is the most appropriate way for us to do.

DR. JANIK: I agree with Barbara with the addition of endometrial necrosis and Ashermans would be an additional thing I would be looking for. I think each new product that you would use for embolization you have to look for these specific questions to see if one product versus another causes more ovarian failure, more Ashermans.

DR. ROBERTS: Can I just ask a question, maybe of Dan, and that is, with the other devices that we are looking at, lasers, cryo, are these specifically approved for the treatment of uterine fibroids or are they just sort of out there?

DR. SCHULTZ: I think the answer is that they are all in roughly the same sort of position which is, again, that a lot of these devices are approved for general uses. The individual labeling may vary a little bit but, basically, they are approved for either treatment of benign tumors within, for instance, the GI tract, the GU tract, the GYN neurology.

Those are the kinds of indications and they are basically more of a tool claim at this point, a general tool claim, and now, as I said earlier, there seems to be more and more of a push in the world of marketing to get specific disease-related or condition-related claims.

That is essentially what brings us here today. So I think that the situation is somewhat comparable and that is why we sort of opened it up to all of these "non-extirpative methods," to try to get some idea.

Again, in terms of the science, not so much in terms of the specific regulatory questions but what we really wanted to hear from this panel was the kinds of things that Dr. Levy was talking about, what are the questions that you guys think are important to evaluate and, from a scientific standpoint, what is the best way to get to those answers.

Then we can use that information to sort of help us design the nitty-gritty regulatory problems. But,

without having that general scientific discussion, we are sort of operating in a vacuum.

DR. ROBERTS: Then I would just ask Dr. Levy, what would be your thought, in terms of the cryo or in terms of those studies? It seems to me you would want to look at adhesions--

DR. LEVY: Right. Those are going to be a little bit different endpoints than these. Adhesions is clearly one. Necrosis. Sepsis, also, in those cases. The same quality-of-life indices. Bleeding; those are being done. Similar indications. The things, as a clinician, that make me crazy is the expansion of the indications become fairly quick to the fibroid is there so we ought to treat it. We want to make sure that we are looking at the complications carefully and that we are controlling in some fashion.

In many ways, it is much easier to control uterine-artery embolization. You guys do write down what you are doing. You do write down what size particles you use. When my colleagues are in the operating room doing myolysis or cryomyolysis, there may be everything from one puncture to 100 punctures into the uterus.

One size bipolar needle versus laser versus freezing probes, and it is a 5-centimeter ice ball or a 6-centimeter ice ball, and it is a ten-minute freeze or a twelve-minute freeze--I mean, the variables are just

tremendous in those kinds of cases.

But I think there are certain things that we need to be looking for as we look at safety first and then at effectiveness. Indications is clear. We need to be controlling for an indicated operative or interventional procedure.

DR. ROBERTS: Would you think that those devices probably would also be handled best with a registry as opposed to a randomization with myomectomy or something--

DR. LEVY: I really do.

DR. ROBERTS: I agree with you. I think that that seems to me like it would probably work a little bit better. If you can't randomize against a hysterectomy, I don't think patients are going to go for it.

DR. LEVY: I just think from a practical standpoint the incidence of complications is low enough in any of these things that a randomized trial would not give us the kinds of data we are really looking for and registry data is going to be much better for us.

If we had a uniform collection form that we used so that we did collect the kinds of data we were interested in, I think that would give us more information than a randomized clinical trial

DR. ROBERTS: I must say, I think we are kind of in an interesting problem. I think, actually, the FDA is in

the same interesting problem, and that is that these things are approved. Any physician who is qualified to use them can go ahead and use them without any concern that they are using a nonmarketed device. It is not even off-label, actually, because it is already approved for the indication that is being used for.

I suspect--quite frankly, if I was one of the companies, I would just sort of say, well, I am not going to advertise this. I am not going to advertise that you can use it for uterine fibroids but the physicians I am selling it to want to use it for uterine fibroids. Okay.

DR. ROBERTS: I think that the studies ought to be done, but I am just saying that the other thing that I am concerned about is if the panel or the FDA says to companies, you are going to have to do a randomized controlled study between hysterectomy and one of these devices, the companies are going to say, well, okay; that sounds nice, but I don't think we will bother.

DR. DIAMOND: That can be their choice.

DR. ROBERTS: But that probably doesn't benefit the patients or the physicians that are using the device either.

DR. DIAMOND: That can be their choice. But the question, again, I think, before us is for the company that does want to have that indication what should that design

be. I think the registry is a great idea as a postmarketing approach to look for rare and unusual complications for procedures that usually are not going to have too many.

But still to find out what is the efficacy as compared to other approaches, I think you need to go back to the randomized clinical trial. It will be hard to recruit, but, again, the endometrial-ablation studies that were done with the newer devices, ThermaChoice and the others. It was the same claims that were made; they were never going to be able to randomize patients to these and, yet, they were able to accomplish it.

DR. BLANCO: Let me take this tack. Who would you use as a control group? Are you going to use a hysterectomy group and how does that compare. I think Barbara brought up excellent points about some of those women are going to get pregnant afterwards. That is not going to happen in the hysterectomy group so how are you going to--

DR. DIAMOND: Now you are at question 2.

DR. BLANCO: No, no. At first, I like randomized controlled trials but the more we discuss it, the more it becomes obvious that, whatever you pick, you are probably going to be comparing apples and oranges and not, necessarily, get the answer you want.

I am also very concerned about what you said. One of the things I heard the patients and a lot of folks talk

about MRI and size and, in this cryomyolysis video, they made a big deal about a 6 percent decrease average in the size of the myoma. That is nothing. I would have been ashamed to have even brought it up.

So I think we need to be careful of endpoints and how many MRIs get done that are not necessary to get done. I think quality of life, improvement of symptomatology and then if we want some sort of control, if you look at a cohort of hysterectomy--there are always going to be women that are going to have hysterectomies for lots of indications and try to match what you are looking for which is complication rates and other concerns.

DR. SHIRK: Again, Michael, you go back to the endometrial-ablation trial. But, again, our initial studies on endometrial ablation were not double-blinded studies with a control. We were using studies that we did early to double-blind back to so I don't think that is a relevant type of thing.

The other thing is the question is what are we asking. Basically, I think the questions that we are asking in this thing are, basically, number one, is the procedure efficacious and, number two, basically what are the complications that occur both to the patient over a long haul, things like does it increase endometrial cancer, does it increase ovarian failure.

Also, the other major issue is, basically, one of reproduction. Certainly, with some of the infertility studies that have been done on follicular-phase kind of failures with low-flow uterine arteries, the question is what kind of reproductive problems are these people going to have if they really do get pregnant.

So I think that there are obviously some significant health issues for women involved with this procedure but I am not sure that we have a good control to compare it to.

DR. BLANCO: A short one. I just want to add recurrence of symptoms; I think it is important over a long time period. I don't think there is a lot of data on what happens five years out. Is this procedure going to have to be repeated every three to five years in order to get some effect whereas, with a more definitive surgical procedure, we won't have a recurrence rate. This would be another issue I would add.

DR. JANIK: Another concern I have is the two groups that seem to have the highest risk of complications with this are either the pedunculated or the submucosal. Both of these groups are very well treated either with hysteroscopic resection or laparoscopic.

So to use the hysterectomy as a control for those subgroups would not make sense in the study design. So I

think you have got, again, a huge problem of what control.

DR. DIAMOND: We haven't gotten to endpoints which is really question No. 2. If I were going to pick a surgical control group, from what I have been advocating, I would probably have picked a myomectomy as opposed to a hysterectomy endpoint.

DR. SHARTS-HOPKO: I was going to speak in favor of a registry approach above a randomized clinical trial. I was going to call to your attention The New York Times cover story yesterday, I think, on women's reluctance to be randomized into treatments that they weren't seeking when they agreed to be in the trial.

MS. YOUNG: I would also like to reiterate--the randomized controlled trial certainly is the gold standard but I think, in the real world, now, where women are more knowledgeable, can get more information about various alternatives and there are more alternatives, I think that women, as Ms. Pearson said, are just not going to be willing to be randomized especially to hysterectomy.

I think that they are sort of increasingly on their way out. Even myomectomy, I think, they would be unwilling to look at that surgical route and be randomized to it.

DR. PERLMUTTER: I have more questions than I have answers. I am concerned about these procedures particularly

in the woman of reproductive age and future child bearing and the incidence of uterine rupture at the time of pregnancy, fetal loss. I don't know how you measure that but if we are going to be using these procedures, that is certainly one of the things that I have to be concerned about.

My other question is for the interventional radiologists concerning the uterine-artery embolization. How do you know these particles get into the fibroids and that you are just destroying fibroids and not normal uterine tissue? Do we know what we are doing to the--or ovarian tissue? Do we know what we are doing to this tissue, which makes me even more concerned about this procedure.

DR. ROBERTS: I guess I can speak to that a little bit. Basically, there are a couple of things. One is that you don't see uterine necrosis, by and large. The incidence of that is well under 1 percent. So, presumably, if you were totally occluding all of the arterial flow to the uterus, the uterus should undergo necrosis and you don't see that.

The other thing that is very interesting is there have been a few patients who have undergone, let's say, CT scans relatively quickly after their procedure. What you find, in that case, is that you find the contrast and, presumably, the embolization material within the fibroid

while the normal uterus looks normal. It is not retaining contrast, suggesting that there is blood flow washing the contrast out of the normal tissue while the contrast within the fibroid is still there suggesting there is no blood flow washing that out.

So that is what gives the idea. It is very similar to what you see in hypervascular tumors in the liver, hepatomas in the liver. You see the same kind of thing with the liver tissue the next day looking essentially normal and most of the contrast and presumably embolic material within the hypervascular tumor.

I will let Dr. Vogelzang also comment if he has a comment on this.

DR. VOGELZANG: We do embolize the whole uterus. It escapes by virtue of its collateral supply and, perhaps, some factors that we don't know yet. But it is a fact. The uterine artery is embolized to stasis and that presumably would account for one of the risks of the procedure which is premature ovarian failure via an embolic route.

But it may be by an endometrial route, at least the Asherman-like syndrome which was alluded. Unanswered questions. In some form, we have to answer those pivotal issues; sepsis, premature ovarian failure, maintenance of uterine reproductive capability. Those, I think, are the big ones, really.

I think, from my perspective, this procedure has been remarkably well safe to date. Keep in mind that we have 1500 or so reported procedures. Probably in the United States, a survey of our members showed that there may have been about 3,000 or more procedures to date with very few reported problems.

I think that is a credit to the training of the interventionalists doing the procedure but, also, a recognition that this organ and this particular treatment is well tolerated.

I, personally, had a little bit of a period where I held my breath as we started this expecting to see, perhaps, that there may be some more problems, having lived through a number of procedures that have been widely touted. I remember, when I was a kid, gastric freezing, for example, for ulcers--all of which have either failed to be efficacious or once an initial blush of enthusiasm in a few centers has been reported, once it gets in wide distribution, there are a lot more problems than people are reporting. This doesn't seem to be the case here.

I think the endpoints that we are looking at here are predominantly the ones we discussed.

DR. ROBERTS: I guess I would make one other comment if I could in terms of the investigations and that might be that maybe this needs to be broken up a little bit.

I think that, by and large, and I am sure there are some people who are touting this as a way to preserve the uterus for fertility, which I think is wrong.

I have done about twenty of these procedures and I have been very clear to the patients that right now we have no knowledge about whether this is the right thing to do in patients who desire fertility.

This might be an area, in patients who do desire fertility, to randomize because their choices are, basically, a myomectomy versus an embolization versus, perhaps, cryo or laser ablation or something like that. That, I think, might be much more appealing to women and, certainly, I think would be a very important place to do a randomization because I don't think we certainly know the answer there.

I think it might be that patients would be more likely to feel that there might be a reasonable place to be randomized.

MS. YOUNG: I have just a quick question. I would like to know the reason for the two deaths.

DR. VOGELZANG: As best I know, the two deaths that have been reported, one, I think in abstract form and the other soon to be published, were related to sepsis, necrotic tumor and the like. One is definitely in the literature as septic. The other, I think in Italy, was,

again, related somehow to that finding.

DR. DIAMOND: I think we are going to go ahead to question No. 2 which we have addressed at some point but maybe we will try to summarize the issues. These are clinically meaningful endpoints and surrogate endpoints if we can't come up with clinical endpoints to utilize.

The first question is what clinical endpoints are available.

DR. SCHULTZ: Before you go on the question No. 2, could I just sort of try to summarize what I think I have heard and maybe you guys can correct me if I am wrong. I heard, basically, three options being discussed. One was a standard randomized controlled trial. Clearly, there were some pros and cons with respect to that.

The other word that I heard sort of thrown around was the idea of a registry and collecting long-term data in large numbers of patients for long periods of time using, hopefully, some fairly standardized models and case-report forms that could include a lot of quality-of-life information in addition to information regarding the specific device and adverse events.

I think that that, hopefully, summarizes it.

Then the other proposal that I heard was the idea of doing some type of matched cohort studies which were prospective and would not require a woman to expose herself

to randomization but, at the same time, try to collect matched data in order to get some information on the various comparisons and things that women are going to want to know in terms of comparing efficacy, understanding that, without the randomization, that those can be a little bit tricky.

I just want to make sure that we are talking about all three of those as potentials and see if there is any further discussion in terms of--as far as postmarket is concerned, I don't think there is any question that a long-term registry would give us a lot of good information.

I guess I am still wondering if there is any more to be discussed premarket or if we should just leave it at that for now and let people come in with proposals and go from there.

DR. ROY: I think registries, postmarket, all that, is fine but I think, fundamentally, what FDA is interested in--what I am interested in--is how do we know what particle size to use. To what extent does one particle size have a greater or a lesser or the same influence on ovarian function or resolution of symptoms, quality of life, things like that? Don't we need to have some fundamental things under our belt before we then go on and do registries, do long-term quality of life, things like that.

Is there a way that we can, in the short term, make some determinance as to what the likelihood of success

is and what the likelihood of improvement is? That is what I haven't sort of heard. I think we all of us agree that it is difficult to do randomized trials. Of course; until you even get a product that you have some assurance is going to be safe and effective, how can you go forward? Who would do a registry under those conditions?

DR. DIAMOND: I had another comment, also, Dr. Schultz, which I wasn't going to mention but, since you brought the topic back up, I will. One issue that I am very much interested in is postoperative adhesion development. There are many clinical problems that occur there. The three biggest ones probably people think of are fertility, bowel obstruction, pelvic pain.

Yet, all the clinical trials to date, at least in OB-GYN, have looked at the infertility patient population because they are the only group where we can come up with a good reason to utilize that as a randomized clinical control study population.

Your thoughts of using the individuals who would like to conceive as the population which, then, might serve as a surrogate for other patient populations, I think is actually a very good one. I guess what I have been hearing most of the panel members saying is that, depending on the indications, maybe we shouldn't require randomized clinical trials if it is hard to do, just do it, one suggestion was,

in the situation where we can look at that issue.

DR. SHARTS-HOPKO: Is it legitimate to select a population desiring pregnancy when you are obstructing a major feeder of the uterus. Is there enough collateral circulation to support a pregnancy?

DR. DIAMOND: That may not be the right cohort of patients to look at in order to do a randomized comparison. Maybe there needs to be a different cohort that is the one that is chosen for exactly those reasons. But it may not be that it will be something that will be able to be applied to all patient populations who might desire this procedure. You may have to identify a very small cohort within that to be representative and to then look for this particular indication.

DR. ROBERTS: I guess if you think about it, if yo you are going to take a patient population that has fibroids that wants to get pregnant--I mean, myomectomy is not a great operation. If you look at the articles that we were given in terms of--I think one was bipolar and the other was cryo--they had uterine ruptures from these.

At least we know that there have been a number of pregnancies in almost all the series that have been reported with, apparently, relatively normal pregnancies. So whether or not they have a harder time getting pregnant, I don't know. But, of course, that is a group that is going to have

a harder time getting pregnant anyway.

So it seems to me, from my point of view, I think that there are enough questions about all of these modalities that I think it is very easy to go to the patient or have the patient hear what all of the possibilities are and say, we really don't know, we really legitimately don't know, what is the best therapy for you.

I think it is easier to tell a patient that than, maybe, your choice is a hysterectomy versus this, and the patient says, well, I don't want to lose my uterus. I have been to all these doctors. I don't want to lose my uterus. I want my uterus. I want something that will allow me to keep my uterus.

That, I think, gets much harder.

DR. BLANCO: Let me add two things. First of all, there is a little--not very large data, but there is a little data from hypergastric-artery ligation which might be comparable that shows that pregnancy, following hypergastric-artery ligation, did not seem to have a lot of major complications.

But, again, it is very difficult to--that study, in the pregnant patient, is going to be just as difficult because you do the artery embolization, you do the myomectomy, but you can't get pregnant right away. You have got to give some time for it to heal and then it is going to

take you a while to get pregnant.

If you are looking at a two-year, three-year, study, again, people get lost to follow up, you are, again, getting into the problem of whether that is a real doable study or not. So I would go back to cohorts and trying to look at the major issue of complications and addressing that.

We can find out how many women get sepsis from this procedure, get infected, how many women that are having hysterectomies get sepsis, get infected, which is a significant number and get some idea--or even myomectomies as the cohort rather than hysterectomies. That might be a more valuable core.

But you are talking about very long studies over long periods of time and the data is going to come out--the hypergastric-artery ligation data that I am aware of was done years after by somebody digging up reports and trying to find out what happened and if they got pregnant. It is going to take years. A registry is probably going to give the answer ten years from now, maybe.

What about endpoints?

DR. DIAMOND: Clinical endpoints.

DR. VOGELZANG: If I could make a comment about clinical endpoints. I think the obvious clinical endpoints here are the symptoms produced by the fibroids. I think we

have discussed that; menorrhagia, pain and others. But, generally, these are all addressed, I think, under the issue of quality-of-life endpoints which are the predominant purpose of the procedure.

There is a proposal underway for development of a quality-of-life measurement which I think would come in probably a little too late for the purposes of this panel, or a study. But it should be available quality-of-life measures that indicate those sorts of things, I think is the principle goal of this, and then the other measures we have talked about which are more physiologic parameters; is the uterus functional, are the ovaries functional, what is the ultimate pregnancy rate, et cetera, et cetera, sepsis, death.

DR. DIAMOND: I think, in some ways, it is going to be hard to look at clinical endpoints. That is not to say that they should not be utilized, but there are some patient populations which will have problems with menorrhagia. There are others which will have different types of clinical types of symptoms and the question then becomes how do you equate all of them into one scale, or do you design a study which is just going to look at one subcategory of those patients which, I think, is probably going to be the more practical way to approach those questions.

DR. SHIRK: But don't you think, Michael, that we are going to have, basically, two problems that we are going to be dealing with as far as clinical problems the patient is going to come in with, either menorrhagia, and we can certainly apply the same kinds of things we applied to endometrial-ablation studies with a Higgam scores and the findings there.

DR. DIAMOND: Exactly.

DR. SHIRK: The other problem is going to be pelvic pain. Again, that is a subjective type of thing that would take some creative kind of setup, but certainly not an impossible way of rating pelvic pain.

DR. DIAMOND: I agree. But the question is are you going to be able to look at both those subgroups in the same study, or are your instruments that you are going to utilize to asses quality of life going to be different such that you need different studies to evaluate them, even if they are parallel studies, perhaps.

DR. SHIRK: You would probably have to do parallel studies.

DR. DIAMOND: That would be my thought as well. You get just one homogeneous population.

DR. VOGELZANG: Keep in mind that many women have both symptoms. I think it would be best to try to measure both parameters in women who have both and the one parameter

in women who have only one of those problems.

DR. DIAMOND: I would agree with you that it is better to measure both and would definitely advocate that. But the question is if you then end up with some patients whose predominant symptom is pain and others whose predominant symptom is menorrhagia, how, from the point of analysis and efficacy, do you capture that?

If, on the other hand, you enter the patient into one of those arms, you could still capture other information.

DR. VOGELZANG: I understand.

DR. ROBERTS: And, of course, you do get into a problem in terms of then going back to exactly what your study is going to be. If you are going to do cohort studies between hysterectomy and, let's say, cryo or embolization or something like that, one place you have a uterus and one you don't. So one you have bulk and one you don't, and one you have got bleeding and one you don't.

So it gets back to, again, somewhat of a difficult thing except for looking at, like, complications, how many infections after hysterectomy, time in the hospital. Those kinds of issues would be certainly what you would have to measure, I guess.

DR. DIAMOND: If you use hysterectomy as your control.

DR. JANIK: I think a core with myomectomy is better, whether it is abdominal, laparoscopic, resectoscope. I think it is a better group.

In addition, I think we need to measure pre- and post-FSH levels and endometrial thickness evaluations to have some sense of proportion of the main thing that we are worried about, safety, along with the study.

MS. YOUNG: I would like to see measurement of some subjective issue such as patient satisfaction.

DR. ROY: I was just contemplating what was just said about resectoscope myomectomies. In the literature provided to us, didn't we have some problems with necrotic aborting myomas as a consequence of the embolization procedures?

DR. VOGELZANG: Yes.

DR. ROY: I think, possibly, that might be a reason not to--

DR. JANIK: That is why I think it is important in the categorizing that we know the location of the myomas. It may be good for multiple intramural myomas, but submucosal may be better hysteroscopically, and then complication, recovery, narcotic use may be much less whereas pedunculated--the death in Europe was from pedunculated from infection and maybe those would be better off treated laparoscopically.

So I think a minimally invasive approach is what is needed but stratifying what patients would be better served is the unknown here.

DR. ROY: I think, from what you just said, it is probably better to have the study devoted to the intramural myomas and not the other two. Let's see if it is safe and effective for that before we go to the other two groups.

DR. JANIK: But I think the way it is marketed and used, it is just myomas all put together.

DR. VOGELZANG: It is not marketed for myomas right now. It is being used for all.

DR. BLANCO: I would add one other thing, and it is not going to happen very often. But when the procedure gets widespread, it will be one of those things that will happen. Sooner or later, one of these procedures will be done on a leiomyoma sarcoma. We need to keep track. Again, it is rare enough that it is going to be a registry issue, not something we are going to be able to study prospectively.

We need to make sure that somebody is looking at that so that, when it does happen, we try to understand what happens with each of these procedures when we hit that.

DR. JANIK: I have a question for the radiologists. Is there any vascular pattern that is different with leiomyoma sarcomas?

DR. VOGELZANG: None whatsoever. There is some suggestion on MR, for example, differentiating adenomyosis from fibroids. But, in general, tissue typing is the holy grail of imaging and we really haven't ever achieved it.

DR. DIAMOND: One additional clinical endpoint that hasn't been mentioned is ureteral obstruction.

DR. VOGELZANG: How many patients really present with significant hydronephrosis or functional ureteral obstruction as opposed to what I usually see which is fullness. That would be a tough one, I think.

DR. DIAMOND: It is not something we see commonly but we routinely will try to get--women with larger uteri get IVPs or have some other assessment of the ureters. It would be something at least to be keeping an eye on. I agree with you; it is not very common.

DR. BLANCO: Let me add one other thing. Not ever having done it, not being a radiologist, it seems that you get a lot of MRIs when this procedure gets done. Is size of importance to anybody. If we get nothing else out of this should we maybe feel like, well, we shouldn't be doing all these MRIs because we don't really care what happens to the size? I am just wondering.

DR. VOGELZANG: I think size is an extremely important surrogate for what is going on here. We relate size by a number of things. Obviously, if a tumor necroses,

it is going to decrease in size. Similarly, symptomatic compression syndromes are related to size. So I think size is a very important thing to measure.

DR. DIAMOND: As a surrogate endpoint; yes.

DR. VOGELZANG: Yes, as a surrogate endpoint. Just by way of background, the reason you see more and more MR is because it is very hard to get precise, objective and, importantly, repeatable measurements from ultrasound unless they are done rigorously by the same person in the same lab. That is just not the case.

The repeatability of the cross-sectional planes achieved by MR is such that you can send them to a core lab and get the kind of repeatable results with a lot of accuracy.

DR. ROBERTS: I would second that.

DR. SHIRK: The cost is significantly greater, too.

DR. ROBERTS: No; that is not necessarily true. If you are comparing a limited MR examination with a transvaginal-transabdominal, which is what you might be getting in someone with a fibroid, it is actually not that much more.

And it is much more reproducible. I would absolutely second what Dr. Vogelzang says that it is much more reproducible in terms of being able to look at the

size, being able to look at the fibroid, being able to look at the relationship with other structures such as the bladder and the bowel. I think it is a much better way of studying these.

So, in terms of a surrogate marker, I would suspect that MR is probably going to be the best way to look at this.

DR. PERLMUTTER: If we are going to use that as a marker, I would make a plea that the pre-procedure marker be done prior to Lupron. I have a lot of difficulty with the articles that were sent to us where the studies were done just pre-procedure after Lupron had been given and then were told that there is a 25 percent increase in volume, but that is normal because that is what Lupron did.

Well, we don't know that. So if you are going to measure whether you have gotten any change, we should do it prior to any intervention.

DR. VOGELZANG: I would agree.

DR. DIAMOND: You probably need both, whether it is Lupron or some other agonist or antagonist that shrunk them as well as where they started from.

DR. PERLMUTTER: That would certainly tell us what these drugs do, which we don't know.

DR. DIAMOND: Exactly.

DR. BLANCO: I would agree with you. I don't want

to beat a dead horse but, earlier in the discussion, everybody said size didn't matter as to whether you did these or not, that what mattered is patient symptoms. So what do we care? If we make it smaller, and the patient is still symptomatic, who cares?

DR. ROBERTS: The only reason, I guess--I certainly know that the FDA sometimes has problems with just using clinical endpoints in terms of symptoms because it is so subjective. You have to use that. You certainly want to use that because that is what it comes down to is the patient being able to say that they feel better.

But, on the other hand, it is sort of nice to have something that kind of goes along with that that you can correlate and say it is not just a placebo type of effect, that really something probably is happening that makes that person feel better.

DR. BLANCO: I would agree with that.

DR. SHARTS-HOPKO: Mike, I am still thinking back several questions when you raised the need for parallel studies based on whether the problem was mainly bleeding or mainly pain. Multiple-regression analysis techniques allow you to have as many outcomes as you want and to track which patient started with pain and how much it was reduced. So that is not an issue, really.

DR. DIAMOND: It is because you still have to

weight them as to relative importance.

DR. SHARTS-HOPKO: Oh, sure.

DR. DIAMOND: As you have two different scales, you have got to say what is equivalent. There is a way to approach it statistically, but you still have to have that consensus, I believe.

DR. SHARTS-HOPKO: Yes.

DR. ROY: You just need to have many more patients.

DR. SHARTS-HOPKO: Which is easier than multiple trials.

DR. DIAMOND: Or, potentially, a sponsor might only do one arm. They wouldn't necessarily have to do both arms, would be another approach. If they could show that it reduced hemorrhage, for example, it could get an indication for that. We might, then, as a clinician, be able to extrapolate that to other indications.

DR. SHARTS-HOPKO: But it is so easy to do both. I don't see why you would not.

DR. DIAMOND: We probably don't want to take a lot more time, but I think just the subjectivity of putting the two scales in parallel and ranking them would make that difficult and subject to a lot of discussion.

Anything else on question 2? Length of follow up to allow premarket approval of these devices. We haven't

addressed that issue at all. How long should we look at outcomes after these different forms of therapy?

We haven't specified a specific outcome. We have given several different options as to what the outcome might be.

DR. PERLMUTTER: But doesn't that really predicate how long you are going to have to follow them?

DR. DIAMOND: If you look at the clinical endpoints you are talking about as far as bleeding or reduction in pain, I would think that could be fairly similar.

DR. PERLMUTTER: I was also thinking about recurrence of fibroids in size and--

DR. DIAMOND: That may be additional fibroids. They may not be the ones that you set out to treat originally regardless of what approach you were taking.

DR. PERLMUTTER: I agree with that, but isn't that part of whether or not she is going to need retreatment?

DR. DIAMOND: It is, but rather than saddling a sponsor with a five-year follow up or a ten-year follow up to get that sort of information, or a three-year follow up, I would rather see a six-month or one-year study with that as part of a postmarket approval if we thought that that was an issue.

DR. PERLMUTTER: Oh; I agree with that.

DR. VOGELZANG: In terms of the immediate issues that we are dealing with which is procedural sepsis and other complications, that is easy. But the issue of premature ovarian failure, in the cases that I have seen or heard reported, that is usually manifest immediately. In other words, failure to resume normal menses within three to four months would prompt that sort of follow up. So I think I would concur, six months to one year should get us where we need to be in terms of most of these questions.

DR. DIAMOND: For the FDA, are there other questions that you are hoping to get out of No. 2? Elisa?

DR. HARVEY: I guess I would pose that question to Dan.

DR. SCHULTZ: I think, again, just to summarize what I think I have heard said so far was in terms of the clinical versus surrogate question, that the panel does believe that the clinical endpoints, specifically bleeding, pelvic pain, are the things that are important and should be measured and really can't be substituted for by simply measuring the size of reduction of the fibroids.

In addition, that the size is a measurement that should be performed in order to correlate those clinical endpoints with an objective measurement but that one would not be substituted for the other.

The other thing that I think I have heard is that

studies of six months to one year probably would be adequate to look at at least the early questions and be able to give women a reasonable comparison of their short-term outcomes to be able to make an intelligent choice as to which treatment would be appropriate for them and that longer-term outcomes could be held off for the postmarket period.

Is that reasonable?

Just one other comment, because there has been some discussion regarding patient selection. There has also been some discussion of different types of studies for use in women who desired fertility and further childbearing as opposed to women who had completed their--and I think that I would encourage the panel to continue to look at those various options.

There is nothing that says that this technology or these technologies or these treatments have to be introduced as an all-or-none phenomenon. I think, actually, one of the things that would be very, very important to look at is if there are certain cohorts--for instance, women strictly with intramural and I don't know what all the right terms are because I am not a gynecologist, but if there are certain subgroups in whom this procedure could be introduced earlier with more of a reasonable idea of safety and effectiveness while postponing introduction in some of these other groups, I think that that is something we would certainly be very,

very interested in.

It might be easier to get to market with those kinds of claims if they were not an all-or-none kind of phenomenon. So I think that I would encourage both the panel and the companies to look at more of a stepwise approach.

DR. DIAMOND: One such group might be individuals who are having a problem with hemorrhage right now because those are not individuals who are going to be able to go through--after failing medical therapy because those are not individuals that are going to be able to just go on for longer periods of time.

Something has to be done right way. Currently, that group, if they have failed medical therapy, they enter surgery of one form or another and, perhaps, embolization or one of these other approaches. That might be something that could be done in that group who needs something done right then and there and then looking at the outcome.

DR. PERLMUTTER: My statement goes back a little bit and has to do with postmarket surveillance. One of the issues, if we go to postmarketing surveillance, might be need for further intervention.

DR. DIAMOND: This is perfect because that is exactly what Question 3 is, postmarket surveillance.

DR. PERLMUTTER: But we would want to know whether

or not people needed further intervention. Our experience with myomectomies is that the probability is that they will. But we would like to know whether it is 100 percent or--

DR. DIAMOND: So, would you recommend a cohort of patients, following approval, be followed or that a registry be established of all patients undergoing any one of these minimally invasive therapies in order to assess that data? What would be your recommendation? Or did I put you on the spot, which I didn't mean to do.

DR. PERLMUTTER: No. Yes; it put me on the spot, of course. The cohort would probably be the nicest but I think you will get your information out of the registry. I guess I am thinking back to this morning's discussion about how are you best going to know whether something is better than something else. Your cohort study will probably do that better than a registry, but I would let the statisticians in the group hassle that one.

DR. ROBERTS: Probably the cohort, to give you the real answer about this, is probably going to be a better way to get the information, particularly if you say you are going to have a cohort of myomectomy patients versus a cohort of cryo patients versus a cohort of embolization patients, for example.

I think it probably makes more sense because, certainly, a lot of the patients that come for embolization

have already had a myomectomy and they are bleeding again. So we know myomectomy is not an end-all, be-all.

So the problem is that that does get into the problem with the registry in terms of the registry data showing you that--for example, you say, well, the embolization or the cryo failed and the patient needs to have another procedure. That happens in myomectomy, too. That is why, although I think a registry is sort of easier and I really don't think that randomization is, honestly--maybe I am biased, but I don't think it is going to really work terribly well.

I think a cohort might work. I think it would depend on how you could set it up. You would have to be really strict, I think, in terms of your indications because you have got to make sure, as best you can--is to match those cohorts. Again, this might be where you kind of get a little bit--maybe this is where it would be important to have sort of the MR data because it might help you to match in terms of numbers of fibroids or whatever.

If you are talking about myomectomy, if you know you took out three of the big fibroids but you left several small fibroids, it would give you something to go on when you got down the line if that is the way it worked out.

DR. JANIK: I do think a registry would probably be helpful. There is enough data in the literature on

recurrence rate and recurrence that requires intervention for laparotomy myomectomy. The question for laparoscopic myomectomy, I think, is a little bit more questionable but we have already a reference point.

DR. DIAMOND: Are there other surrogate markers that we would want to have followed as part of a postmarket approval study that we haven't already mentioned? Are there long-term sequelae that we are worried about?

DR. SHIRK: I guess one thing I am worried about is the issue of endometrial cancer basically because of the studies of Gus Wami and those guys on patients with follicular-phase defects and poor uterine-artery flow as in fertility patients.

But they did show that there was some significant endometrial disynchrony in those patients. These patients are already patients that have disynchronous endometrium. As a question, does this carry on into premenopausal patients, or patients in their forties who have significant reduction in uterine blood flow.

Certainly, you see that as a reproductive endocrinologist, problems in getting people pregnant and selecting people out in that age range who would do well with IBF and who wouldn't. So I think it really is a long-term issue.

We had a lot of that when we were doing the

endometrial ablation. Everybody was up in arms about, are you going to hide an endometrial carcinoma, or is the laser going to cause a problem. But I think, in this situation, the questions of what we are really doing to endometrial growth are a big issue over time.

DR. DIAMOND: Another issue that I would worry about over time and would hope that postmarket studies could show is what happens as far as pregnancy outcome, of those individuals who conceive, what the miscarriage rate is, what happens as far as rates of pre-eclampsia which is thought to be due to vascular insufficiency, timing of delivery, types of placentation, if you have more placenta accretas or other adverse pregnancy outcomes, just to sort of summarize them.

DR. ROBERTS: Of course, this would go back to the issue of whether or not you are taking patients that want fertility versus patients who don't want fertility but want to keep their uterus and don't want bleeding, or pressure symptoms, or whatever.

Again, I think it is going to be a different group of patients. That, I think, is going to be the issue is which group are you going to study. That, I think, is probably for the sponsors to decide what they want to do in terms of looking at patients.

DR. DIAMOND: But even if you have a group of women who do not wish to conceive, since fibroids are

primarily a tumor of the reproductive years, there will always be the potential that individuals who did not plan to conceive, unless you insist on tubal ligation or some other form or sterilization at the time of the surgery, or at the time of this procedure, some of them may conceive.

Then the question is what is the outcome, and to be able to provide that information for the future.

DR. ROBERTS: That is just sort of longer-term.

DR. ROY: Dr. Shirk, how would you propose assessing the endometrium in those patients in terms of follow up? Would it be endometrial biopsy? Would it be endometrial echo complex? What would it be?

DR. SHIRK: If we are just using a registry, obviously it is a reporting type of situation. I think that, again, the question is how long can you keep a registry, or companies to the fire as far as reporting into a registry. These may be long-term complications in these patients although, certainly, a lot of the patients that are going to be treat with the procedure are going to be patients that are in their forties because that is when we see most of the fibroids that are symptomatic, the bulk of them are patients who are in their late reproductive life.

So that may not be such a long time, but I was thinking more of just a registry follow up in these patients.

DR. VOGELZANG: If I could make one sort of overview I see on the next few questions. I believe it would be unlikely that any of the indications for this would include, given the state of knowledge and the difficulty it is going to--the problems involved in looking at this long-term that this would ever be indicated as initial pass-through for women who are of childbearing age or wish to have children or haven't started their families yet.

I think what we are looking at here is a population of women who have made their fertility decision and for whom fibroids are a problem, and we are going to have a subset of those who may become pregnant.

I think it is going to be difficult to advocate or to even do an appropriate trial in which you would submit women who had not started their families, had fertility decisions yet to be made.

DR. DIAMOND: The other surgical techniques, such as a cryomyolysis, the bipolar electrocautery, there are colleagues of mine who are advocating it as the front-line therapy for fibroids in those situations.

DR. ROBERTS: The other things you have to look at are things like bowel obstructions from adhesions and things like that as well in terms of complications down the road. The problem with those is they can be years later, too.

DR. DIAMOND: Barbara, before she left, had made

the comment that she was concerned with cryomyolysis, I believe it was, about post-operative adhesive development. But we don't have a real good way of assessing that unless you do another operation. Are we advocating that specifically to look at that endpoint? I don't think I would have.

So you are looking at the clinical endpoints leading to potential complications from the procedure as opposed to visual identification.

Again, the question is how long should these postmarketing studies go on. Five years?

DR. ROBERTS: Sorry; we were saying forever over here.

DR. BLANCO: I think you have to identify the endpoints and make it according to when your endpoints are going to show. It may be forever on some things.

DR. DIAMOND: Cindy, this is your turn to say something.

MS. DOMECUS: SCVIR has already started their registry so I was hoping it wasn't going to be just the burden of industry.

DR. ROBERTS: The problem is that the FDA is the one that is going to make the decision in terms of the company's labeling as to how long they have to carry out the postmarketing surveillance. You have to reasonable about

it. I can't imagine, except for maybe the patients that--you are certainly not going to follow everybody from the time the thing is, let's say, approved for uterine-artery embolization, you are not going to follow the new patients after that.

Maybe you follow the ones that have already been enrolled for a year or so. At least some of them will have already been out, the way these things go--will probably have already been out a number of years by the time you get the study done. So I don't think you can probably ask for a whole lot more than that.

DR. DIAMOND: Depending on the endpoint, I would have said three to five years, probably.

DR. VOGELZANG: I would agree. In terms of the long-term things, in terms of likelihood of achieving pregnancy and outcome of some of the pregnancies that are achieved three to five years--I think you have to look, certainly, beyond a year. And the typical endpoints are three years or so.

DR. DIAMOND: Do you want to summarize question No. 3, Dan? Let's go on to 4?

DR. SCHULTZ: I think you can go on to 4.

DR. DIAMOND: Now the question before us is inclusion and exclusion criteria with respect to a variety of premises that have been given to us; fibroid size,

parity, pretreatment, GnRH use--this says agonist, but antagonists are now available in this country as well--menopausal status, previous gynecological procedures, adenomyosis, leiomyoma sarcomas, other potential confounding factors.

DR. ROY: You can exclude the leiomyoma sarcomas; right?

DR. DIAMOND: If we know it is a leiomyoma sarcoma, we want to exclude those patients; yes.

DR. ROBERTS: The chances of you knowing that are--

DR. DIAMOND: Are not good.

DR. ROBERTS: Not very good. But I think the things that you certainly want to exclude are patients who you know have an endometrial cancer. So, because you are going to presumably going to operate on those patients and they should get a hysterectomy, I would assume so. With those patients, probably they are going to need an endometrial biopsy, I would think, in all the patients, no matter what group you are looking at.

DR. DIAMOND: I wouldn't necessarily say that. If you have a young woman, normal body weight without other risk factors who has regular menses, very heavy menses, I would have let that more to their discretion as opposed to mandating that as a routine requirement.

DR. ROBERTS: Okay.

DR. DIAMOND: Minimum fibroid size? Symptomatology is what we said already is the most important thing. So they have to have clinical symptoms. Minimum fibroid size accounting for those symptoms? They have a 1-centimeter intracavitary myoma. I would have trouble, also. Not that I know where I can draw the line, but that is why I chose one that was going to be obvious.

DR. ROY: Some of those intracavitary lesions are pretty broad based and they don't lend themselves, really, to reliable hysteroscopic success at its removal. So I don't know; the angle with which it enters the endometrial cavity. People argue about that, whether it is acute or oblique. But that doesn't really, necessarily, relate to size.

MS. DOMECUS: But if you only getting patients who are symptomatic, does it matter what the size is?

DR. DIAMOND: You end up with a very heterogenous type group. We talked about bleeding and submucosal fibroids.

DR. BLANCO: Actually, you do need to measure size although I facetiously was asking about that because your complication rate--if this works by necrosing the fibroid, if you do a 20-centimeter fibroid and they give you a lot more symptomatology after the fact--I don't know; maybe

there is some data already from our radiology colleagues whether size of the uterus affects symptomatology in terms of recovery. You have got, you would think, just a lot more necrosed tissue to get rid of.

DR. VOGELZANG: It would seem, but it is not clear at this point in time, that that post-procedural recovery is prolonged if they are excessively large. At the extremes, I suppose that would be true, but for the broad middle part, two standard deviations around the mean for symptomatic fibroid size, I haven't seen anything correlated yet.

MS. DOMECUS: I wasn't saying that measuring them wasn't a good idea. I am just saying do you really want to exclude from the study patients with fibroids of any particular size as long as they are symptomatic.

DR. VOGELZANG: I do not believe you should because I think we know that fibroids usually are of a certain size when they become symptomatic. There are some exceptions, but I don't think exclusions based on size would be prudent here.

Neither do I believe that exclusions based on location is a particularly relevant question mainly because it is not known. In other words, there are reports of spontaneous expulsion of fibroids, submucosal fibroids, or intracavitary fibroids, but the therapy seems to be effective for them as well.

There does not seem to have been a cohort of patients whose fibroids are not treated, for example, by uterine-artery embolization. So I am not in favor of segmenting that population. We don't know.

DR. JANIK: I think we don't know but I think it will become more clear who is best. I think we just need to make sure our cohort matches both in size and location, both factors, and number.

DR. DIAMOND: Do we believe these procedures should be done on postmenopausal women?

DR. VOGELZANG: No.

DR. DIAMOND: I would say no. I think the risk of a leiomyoma sarcoma in that group is going to be significantly higher.

Prior myomectomies; is that a reason to exclude patients?

DR. VOGELZANG: No; I don't believe so.

DR. DIAMOND: Adenomyosis? Are we going to be able to differentiate adenomyosis as well?

DR. VOGELZANG: I think you can make a stab at it based on MR but that, again, assumes that every woman is going to have an MR. Adenomyosis is, as I understand it, a difficult diagnosis to make clinically and differentiate it from fibroids. My understand is that, in a few cases that I have been shown and heard about, adenomyosis proved to be

the cause of "failure" of uterine-artery embolization of fibroids because it wasn't treated.

DR. JANIK: But in myomectomy, it is a failure, too, so it will be the same in both groups. So it should be okay.

DR. VOGELZANG: That's true. So I wouldn't make it--

DR. DIAMOND: But I think, in cases of failure, you want to try to get tissue for evaluation and know what that shows.

Shall we require a biopsy of fibroids prior to treatment?

DR. JANIK: No.

DR. DIAMOND: I don't think anyone is advocating that.

DR. JANIK: There are people who do it, but I think it is an extra procedure and it is not warranted.

DR. DIAMOND: GnRH use. We talked about before that if you are going to use GnRH or other means of ovarian suppression that it be important to know size, both before and after therapy, before going to the surgical modality that is going to be used.

I would have left to the discretion of the sponsor whether to allow its use or not and whether it can be a mixed bag or whichever you choose needs to be an all-or-none

situation.

DR. BLANCO: I thought it maybe shouldn't be used just because it adds another variable to the study that you are going to have to look at if you end up with a third of your women having some medical treatment that make their fibroids smaller and then go to the procedure. It may just complicate your data and you may need more numbers.

DR. DIAMOND: It might, but current clinical use, probably with the exception of embolization, would involve current use of an agonist or some sort of suppression to shrink it in order to minimize what has to be done at the time of surgery.

DR. JANIK: I agree and we know that post-agonist therapy, you revert back. So I think just as long as you have a baseline pretreatment, you would be fine.

DR. ROY: Do the radiologists know whether the myomas respond better without agonist therapy or after agonist therapy?

DR. VOGELZANG: It is a good question. The general feeling among many of us treating these patients is that we are better off without Lupron on board, certainly, Lupron active either in Depo form or monthly therapy. The reason is it reduces uterine blood flow.

The uterine arteries are small. I had a patient, for example, not long ago who, for whatever reason, had been

on Lupron for quite some time and her uterine arteries were extremely small, so much so that we declined to even proceed. We didn't even catheterize them.

So most of us would prefer Lupron not to be actively in place because it reduces blood flow and we believe may reduce effectiveness of the fibroid embolization.

DR. DIAMOND: I guess the other issue that goes along with that is needing to know what the use of GnRH analogues are after the procedure at the time that the endpoint is being assessed as well, whether it is in place or not and whether there is add-back therapy or not in order to level the playing field.

Other confounding factors?

Part (b) of this question is there are some women with single fibroids. Others have multiple fibroids. Probably individuals with multiple fibroids have a higher rate of recurrence than individuals with a sole fibroid. Should this be another factor?

DR. VOGELZANG: I don't believe so because the disease tends to be--multiple fibroids tend to be the rule not the exception. I think it would be extremely hard to sort of segment the population that way, the study population that way.

DR. SHIRK: The only place where it might be a

problem would be in cryomyolysis and other myolysis procedures where you have got multiple small fibroids you are trying to drill different holes into and does that increase the risk of adhesions and postoperative complications just from the trauma done to the uterine wall.

DR. DIAMOND: Actually, with an 8-millimeter probe, which is what they were using for that, what do you do with fibroids that are smaller than that size, or ones that are less than the 5 centimeters that they said where they worry about the ice ball getting outside to normal myometrial tissue. That would have to be addressed.

DR. BLANCO: I just would add it may actually be a bit advantage of embolization. If you are embolizing the entire uterus, and the fear is that the myometrium and the endometrium are okay because you have got collaterals whereas the myomas have single vessels going into it that you occlude, embolization may treat all of the multiple myomas and may cause less recurrence.

So I don't know that it is that firm an endpoint but it may be something interesting to look at in terms of showing whether the procedure might actually be better than a myomectomy resection or something like that.

DR. ROY: You are an obstetrician, aren't you, not a gynecologist.

DR. BLANCO: I am here to be fair.

DR. DIAMOND: Any evidence, at this point, that undergoing one of these procedures might make subsequent procedures more difficult or complicated?

DR. VOGELZANG: I don't think I have heard of subsequent myomectomies--certainly hysterectomies. But in the reported cases, it has not been worsened because adhesions are produced. But myomectomies, I just don't know. Frankly, I think we are not out far enough to really have had enough recurrences if they really are a problem.

DR. JANIK: And some of the hysterectomy reports are active-infection situations so they have been terrible hysterectomies.

DR. VOGELZANG: Correct.

DR. DIAMOND: Is it worthwhile to try to look at doppler flow studies of uterine vessels before the study, before the procedure, and then months afterwards? Is that going to give any information as to adequacy of the procedure, looking at uterine vessels or the periuterine vessels?

DR. VOGELZANG: Again, I think an interesting observation but not one which I think you could reliably get given the vagaries and the individual qualities of a doppler interrogation of the pelvis which would have to be transvaginal, plus transabdominal, and be done by a skilled group of people.

So I would tend to put that in the interesting category but not data which you can ask to be derived.

DR. ROBERTS: I think it gets back to this issue of how much to depend on clinical endpoints versus sort of objective surrogate endpoint. My feeling has always been that clinical endpoints are probably the most important because that is what the patients are going to see as a modality or a device gets put into wide application is that is the bottom line, how do patients do with it.

I think it is helpful to have some surrogate endpoints that are more objective that you can measure but I kind of agree with Dr. Vogelzang that trying to get a doppler ultrasound looking at the blood flow to the uterus, I am not sure what that tells you besides the fact that there is blood flow there which you would probably know.

DR. ROY: It might be useful if you were able to know that before you catheterized her and found the vessels to be too small to utilize.

DR. ROBERTS: But if you have done a history and you know that the patient is on Lupron or another drug that might impact that, yes, that may tell you you may have a problem. Maybe at that point, you are going to go and look and see. But, by and large, almost all of these patients have very large uterine arteries and it would be another piece of information but relatively expensive.

You can see that, at least to some degree, on the MRIs in terms of some indication of blood flow depending on how you do it.

DR. DIAMOND: Is there any reason to think that women with uterine anomalies or DES uteri would be expected to have different outcomes with any one of these modalities where they ought to be included or excluded?

DR. ROY: Dr. Perlmutter says she has never seen fibroids in a DES-exposed uterus.

DR. JANIK: Neither have I.

DR. ROY: How many DES-exposed uteri have you seen recently?

DR. PERLMUTTER: I come from Boston.

DR. ROY: I am saying it to the rest of us.

DR. PERLMUTTER: You are seeing those ladies age now, so you are seeing them in their forties and fifties. I honestly don't remember seeing a fibroid in that group.

DR. DIAMOND: Anything else from question 4?

Let's go to 5. This is something that we have already addressed to some extent but, specifically, in both conceiving and maintaining pregnancy, after patients have undergone these procedures, is not well understood. Should there be requirements on labeling, study limitations, postmarket requirements that can address this issue? Should there be a specific warning regarding women of childbearing

age?

MS. YOUNG: Yes; I think there should be. Also I think that, going along with that warning, should be some information about uncertainties of the device in terms of future childbearing pregnancy outcome and some of the other things that were--just stated in sort of a general way, but it seems that there are sufficient uncertainties about it that women should be told what those are.

I say that knowing that, as is usually the case, realistically, women are not told what the uncertainties are for a specific treatment or device.

DR. SHIRK: I guess this is one place where I could see a double-blinded controlled study type of thing using myomectomy as one control arm and the procedures as the other control arm so that if the companies are interested in pursuing the ability to advocate that these can be used on patients with pregnancy that you really could set up a significant controlled study.

I guess I would certainly advocate that we think about that if we are going to--it certainly has some hazards in that these pregnancies may be fairly complicated, but, also, if you do a myomectomy, you run the risk of having the patient have a uterine rupture and antepartum and other complications, too. So it is the initial pathology that is the problem.

DR. DIAMOND: We also know that we worry about adhesion development to the uterus after myomectomy, particular the posterior. The concern is that that may, then, create infertility for both the tubes and the ovaries.

DR. JANIK: But these patients have adhesions, too, the embolization patients.

DR. VOGELZANG: Yes; they have had myomectomies. They have had other therapies, and so on.

DR. DIAMOND: But a group that had not had prior therapies might be expected to have less.

DR. VOGELZANG: Yes.

DR. SHARTS-HOPKO: I don't see a controlled clinical trial in that case, either. I think that most women who desire pregnancy, this has been a difficult thing for them. If it is more women in their forties, most of those women don't desire pregnancy. I still think this is a registry follow-up issue with a warning that we do not know how able they will be to carry a pregnancy.

DR. DIAMOND: I can tell you there is a whole host of patients I see in their forties who want to conceive and even some now beyond that with donor eggs and that availability.

DR. SHARTS-HOPKO: There are many out there, but I don't think it is a majority.

DR. DIAMOND: I would agree.

So, labeling? It sounds like, from the comments now and the comments before, if this is going to be done in someone who desires future childbearing, it sounds like there ought to be labeling that we don't know what is going to happen and what the outcome of those pregnancies would be.

DR. BLANCO: Let me throw something in. We are going to label this device that a physician is going to use. So are we talking about labeling aimed at the physician or are we talking about labeling that something comes in with a kit of the whatever, powder, et cetera, that has to get handed over to the patient for her to read when she is going to undergo the procedure. So I think we need to separate the two types of labeling we are talking about.

DR. VOGELZANG: I would say both, at this point in time.

MS. YOUNG: And the patient insert, or whatever you want to call it, should have the risks of the procedure. It always includes the benefits, how it works and so on, but it must also include the risks, side effects, what women should look for in the event of possible complications, fever, whatever, additional bleeding or pain, unusual pain.

DR. ROBERTS: That is what will come out of the study. Once the study gets done, then you will be able to say to somebody what the risks are in a much more controlled

fashion than you can now.

I agree. I think that if we are going to say that this is something that ought to be--the only way to say that this is something that is safe and effective to use in women who want to get pregnant is to do it in women who want to get pregnant is to do it in women who want to get pregnant and see whether or not it is safe and effective in whatever it is, whether it is cryo or anything else.

If you want to market it for patients who want to get pregnant, then you better do the study to show that, in fact, patients who want to get pregnant, that this is safe and effective.

I don't disagree with the fact that there will be women who end up getting pregnant but that is different than marketing it and saying that it is a safe thing to do in patients who are trying to get pregnant. I think that is the difference. Otherwise, you just sort of say, we are not really sure how safe this is in pregnancy.

DR. DIAMOND: I think George's question actually is a very good one. And while I agree in principle that we would want to let the patients know about this, I can't think of an example of a device that we utilize, other than maybe an IUD, where we give information to the patient about the device as opposed to the healthcare provider.

Is that what we are recommending?

DR. ROBERTS: For example, going back to the stent grafts, they mandated that there will be patient education materials that will be handed out to the patients prior to undergoing those procedures, is my understanding.

DR. BLANCO: You brought up the other one, IUD and endometrial ablation. We did make a patient package. I don't think that is out of line at all. I think that that is something that the patient needs to know.

MS. YOUNG: I think women want that information. It is very easy to sit in a clinic situation and having your physician or someone explain the device to you. It's true because I have experienced it. You are hearing what is said, but when you go away, you can't retain all of that information at all and it really, I think, is essential, for women to be able to make informed choices, for them to have key information about that device.

DR. BLANCO: I think we can do that. Most people seem to be shaking their head yes. Going back to the pregnancy, I agree with you. I think there are two issues. One is some of these people are going to get pregnant, not meaning to, and that is going to be great data. But I think that there is going to be more, and maybe this is because I am an obstetrician and I see a younger population or people who are still getting pregnant--but you see infertility. Don't you see a significant number of patients that have

fibroids that that may be the cause of the infertility?

They would be perfect. They would be the ones you want to study to have an indication this is better than a myomectomy because there is no scar, it may have a lower rupture rate. It could turn out to be better. So I would think that that would be a study where you could get--and there you don't have the bias of women--because we don't really know is one better than the other, one more invasive than the other, but there may be more knowledge about one, the myomectomy, than the other and you could get women randomized and really see which gives you better outcome, better pregnancy rates, and so forth.

DR. DIAMOND: I guess the last question here, should women who undergo these procedures be followed--and this is talking about women of childbearing age--be followed until menopause or conception regardless of the length of follow up that would be required.

MS. DOMECUS: I would strongly disagree with that. I think the three to five years postmarketing surveillance data we have already talked about is kind of on the outside of the range that would normally be expected. So I think this could potentially be significantly past that. I think this would be unduly burdensome.

DR. BLANCO: It could potentially be twenty years. You are not going to have any follow up. Maybe if you live

in Framingham, whatever, but unless you have some sort of a huge system, it is going to be very difficult to follow people until menopause.

DR. VOGELZANG: Not mandated, but I think the medical-research community will always pursue questions like that. Interested investigators will look into those matters.

DR. JANIK: I have one comment back to the cohort study design. I think, in addition to the things mentioned, narcotic use, discharge time and return to work should be included. There is, even in this panel, an underlying assumption that embolization will be less narcotic. But I am not sure that even that is necessarily the case. So I think we need to have that data. I think, in some cases, they use more narcotic.

DR. PERLMUTTER: Including febrile episodes, since some of the studies show that you can be febrile for a minimum of two weeks after the procedure.

DR. JANIK: Right. And from laparoscopic and hysteroscopic procedures, people are out in a day, back to work in a week. And their narcotic use is probably less. So if we are marketing and targeting patients to make them think this is quicker, they can get back to their jobs, it may not be true. So I think we need that data.

DR. ROY: Did you mention antibiotic usage,

because with the fevers, although they may not be true infections but more reflective of necrosis, I think many of the reports I made, they did administer antibiotics anyway. So that is also important.

MS. DOMECUS: I just wanted to clarify. We have talked about some things that should be studied in the postmarket-study scenario and others in the patient-registry scenario. I think that since SCVIR has already started the registry that those things that we have talked about for study in a registry situation can be done by them and the sponsors and the manufacturers of the devices can be responsible for the things we have talked about, or postmarket study, and they shouldn't have to also do the registry since that is already underway and can probably more appropriately be done by that group.

DR. ROBERTS: The only issue will be what is in the registry or what is being collected in the registry is what the FDA wants to see as a registry data. That is the only concern that I have. There is always this tension between what the academic or practicing physicians want to see in terms of registry data and what the FDA needs to see in terms of marketing approval.

So, if that is the case--I am not saying that it shouldn't be--but, if that is the case, then there needs to be communication so that if somebody is doing a registry,

the FDA can just take that data. Well, the FDA might not want to just take that data. I will leave that up to Dan Schultz.

DR. ROY: Not just that, but what we are talking about isn't just a registry for the purposes of--

DR. ROBERTS: Exactly.

DR. ROY: It is for these other procedures.

DR. DIAMOND: Other procedures, as well.

I think we have answered question 5.

DR. BLANCO: In that case, if you will turn it back over to me, I think we shall try to wrap it up. It is not quite 5 o'clock yet. I don't know if Dr. Harvey would like to say a few words. I would like to thank all of the panel members and the public for all their comments and all the information.

Would you like to make any comments? Unless there are any other items, we will close the meeting.

DR. SCHULTZ: Before you do that, Dr. Blanco, I would just like to say thank you to you and to the other members of the panel, both the gynecologists and to our radiological colleagues for coming down here and discussing and giving us what I think was a very helpful, productive session and a lot for us to think about in the days and weeks to come.

So thank you very much.

[Whereupon, at 4:55 p.m., the meeting was adjourned.]

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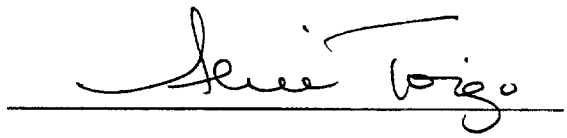

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